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Effects of Therapy With Nifedipine GITS or Atenolol on Mental Stress-Induced Ischemic Left Ventricular Dysfunction

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Objectives. **We sought to determine the effect of nifedipine gastrointestinal therapeutic system (GITS) or atenolol on ischemic left ventricular dysfunction induced by mental stress.**

Background. **The efficacy of conventional antianginal therapy in preventing myocardial ischemia induced by mental stress is unknown.**

Methods. **Nifedipine GITS, atenolol and placebo were administered to 15 subjects with stable angina in a double-blind crossover trial. Subjects underwent a series of mental stressors at the end of each treatment. Radionuclide ventriculography was performed at baseline and at peak mental stress. Other measured variables included time to ischemia on exercise treadmill testing, ischemia on 48-h ambulatory electrocardiogram (ECG) monitoring, and resting and mental stress-induced levels of plasma catecholamines, tissue plasminogen activator antigen, plasminogen activator inhibitor-1 and platelet aggregability.**

Results. **Mental stress resulted in a significant increase in plasma epinephrine and norepinephrine levels during each treatment phase. Atenolol therapy was associated with lower baseline and postmental stress rate-pressure product compared with nifedipine or placebo. Therapy with either nifedipine GITS or atenolol prevented the development of wall-motion abnormalities and the decline in regional ejection fraction (EF) in the segment with the largest deterioration in wall motion during placebo therapy. Both medications prevented the decrease in global EF in subjects who demonstrated at least a 5% fall in global EF on placebo therapy. No therapy exerted a statistically significant benefit on exercise performance or frequency of ischemia during ambulatory ECG monitoring.**

Conclusions. **Both nifedipine GITS and atenolol are effective at preventing mental stress-induced wall-motion abnormalities, although the mechanisms may be different.**

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Psychological factors negatively affect the clinical course of patients with coronary artery disease (1–13). For example, episodes of anger during daily life may induce myocardial ischemia and infarction (6,10,11). Psychological stress associated with natural disasters such as the 1994 Los Angeles earthquake (13) or wartime stress (14,15) may trigger acute ischemic syndromes. Myocardial ischemia may be caused by the catecholamine surge that accompanies acute mental stress by increasing double product or inducing coronary vasoconstriction (16). Acute myocardial infarction may be triggered by catecholamine-induced plaque rupture or by induction of a hypercoagulable state with resultant coronary thrombosis (17–19).

Experimentally, mental stress can be induced by a variety of stimuli such as a stress interview or simulated public speaking (1,8,11,20–26), performance of mental arithmetic (1,7,8,11,25–29) or the Stroop color word test (1,8,11,20,26,30). In some patients with coronary artery disease, mental stress induced by these procedures is associated with a significant decrement in overall ejection fraction (EF) and/or new abnormalities in regional wall motion on radionuclide ventriculography (1,8,11,20,26,30) and less frequently with transient ST-segment depression on ambulatory monitoring (2,28). In addition, mental stress can induce transient perfusion defects on

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Abbreviations and Acronyms

ADP = adenosine diphosphate
AECG = ambulatory electrocardiography
ECG = electrocardiogram
EDV = end diastolic volume
EF = ejection fraction
ESV = end systolic volume
NYHA = New York Heart Association
PAI-1 = plasminogen activator inhibitor-1
SV = stroke volume
tPA = tissue plasminogen activator

SESTAMIBI scintigraphy (29) and angiographic coronary vasoconstriction (24).

The effects of anti-ischemia medication on myocardial ischemia induced by mental stress has not been well-studied. Some advocate beta-adrenoceptor blocking agents to limit the increase in heart rate and blood pressure induced by mental stress, whereas others suggest that calcium-channel antagonists targeting the prevention of coronary vasoconstriction may be more appropriate therapy. The purpose of this study was to investigate the effects of nifedipine gastrointestinal therapeutic system (GITS) or atenolol on ischemic left ventricular dysfunction and alterations in coagulation status induced by mental stress. Serial "mental stress testing" was used in a crossover design to allow for serial drug testing with nifedipine GITS, atenolol and placebo. Assessment of wall-motion changes by radionuclide ventriculography in response to mental stress served as the primary end point; secondary end points included the effect of these medications on left ventricular diastolic function, platelet function and fibrinolytic activity in response to mental stress.

Methods

Subjects. Subjects were recruited from the outpatient cardiology clinics at the Brigham and Women's Hospital, Boston. Inclusion criteria included age between 35 and 75, history of stable angina pectoris, a positive exercise treadmill test (defined as >1.0 mm flat or downsloping ST-segment depression induced by exercise), coronary artery disease documented by coronary angiography or by prior transmural myocardial infarction, and >2 episodes of ischemia on baseline 48-h ambulatory monitoring. Exclusion criteria included a history of myocardial infarction or unstable angina within 3 months of study entry, uninterpretable ST-segment morphology or concomitant severe illness. The institutional committee on human research approved the study protocol.

Study protocol. This study was a randomized, double-blind, placebo-controlled crossover study lasting 13 weeks per patient. After a 1-week single-blind placebo run in-phase, subjects were randomized to the first of three, 4-week-long treatment regimens: nifedipine GITS (mean daily dose 88 ± 22 mg), atenolol (mean daily dose 91 ± 20 mg) or placebo. Medications were titrated to maximally tolerated dosages during the first 3 weeks of each 4-week regimen, and at the end of the 4 weeks, the subjects were admitted to the Clinical Research Center for testing. In a similar manner, subjects completed two additional 4-week regimens in random-order sequence.

The Clinical Research Center protocol involved an afternoon admission and application of an ambulatory electrocardiogram (ECG) monitor with sleep beginning between 10 PM and midnight. Subjects were awakened the following morning at 8 o'clock, remaining supine for vital signs and blood tests and transported to nuclear medicine for resting radionuclide ventriculography and mental stress testing. During mental stress testing, skin conductance level, heart rate, blood pressure, stress and angina ratings were continuously monitored, and the ambulatory monitor was continuously applied to monitor for ST-segment depression. At peak mental stress as determined by skin conductance, radionuclide ventriculography was repeated. Following mental stress testing, subjects ate and remained sitting for 2 h, followed by blood tests and repeat vital signs. Finally, an exercise treadmill test was performed with blood tests at peak exercise. After exercise testing, subjects were discharged for an additional 24 h of ambulatory ECG (AECG) monitoring, and then crossed over to the next medication regimen.

Mental stress testing protocol. The mental stress protocol consisted of three tests as described by Jacobs et al. (31): 1) 5 min of pressured arithmetic consisting of serial subtraction of 7 from a four-digit number with pressure to subtract faster and criticism of mistakes; 2) Stroop Color Word test for 5 min consisting of a sheet with four columns of words "red," "green," and "blue" printed in ink of a nonmatching color with instructions to name the ink color as quickly as possible; and 3) a stress interview for 5 min in which subjects were asked to discuss the area of their life that had been the most stressful, with the interviewer probing the most emotionally laden aspects of the patient. Mental arousal was monitored with skin conductance level measured every 15 s with a Davicon C20 EDR (Davicon, Burlington, MA). Mental stress was titrated by a psychologist to achieve a similar level of increased skin conductance during each drug phase.

Radionuclide ventriculography. The subjects' red blood cells were labeled with 740 Mbq (20 mCi) 99m-technetium by means of a semi-in vitro technique. Data were collected with the use of a 20% window at 140 keV on a large field-of-view camera (GE) equipped with a low energy, general purpose, parallel-hole collimator. Six million counts were acquired in the best septal left anterior oblique projection with 15-degree caudal tilt. Software zoom ×2 was used to minimize counts from noncardiac structures. A gate interval of ±10% was set, and the studies were acquired in frame mode, 24 frames/cycle, in 64 × 64 word mode. The studies were spatially filtered frame by frame with a two-dimensional fast Fourier transformation.

An algorithm with automatic edge detection and automatic background correction was used for computing the volume-equivalent left ventricular time-activity curve. The

resulting time-activity curve was temporally filtered by fitting a four-harmonic series. Global systolic and diastolic function expressed as: EF = (EDV [end diastolic volume] − ESV [end systolic volume]/EDV) × 100%, peak ejection rate (PER) in EDV/s units, peak filling rate (PFR) in both EDV/s and SV (stroke volume)/s units, PFR/PER ratio, and time to peak filling rate (TPFR) in milliseconds were computed. Regional EF was determined by standardized computer-assisted division of the left ventricle in six portions, the outflow tract region was excluded, and for each of the remaining five regions, time-activity curves and regional EF were generated. Wall-motion values for each of these five regions were also scored visually by two independent observers by consensus using a 4-point scale: 3 = normal, 2 = hypokinetic, 1 = akinetic, and 0 = dyskinetic. Change in wall-motion score and regional EF during nifedipine and atenolol treatment was determined for the left ventricular segment with the greatest deterioration in wall motion during the placebo phase for each individual subject ("worst segment analysis"). Finally, subjects were divided into two groups based on whether global EF fell at least 5% with mental stress (EF responders and nonresponders) (11,21,32) and analyses were repeated.

Exercise testing and ambulatory ECG monitoring. Exercise testing was symptom-limited using the standard Bruce protocol. Ambulatory ECG (AECG) was performed with Applied Cardiac Systems cassette recorders (Laguna Hills, CA) and modified leads V5 and aVF. The ECGs were analyzed on a CardioData MK4 playback system with modified software (33). An episode of ischemia was defined as transient ischemic ST-segment depression of at least 1.0 mm, lasting at least 1.0 min, and separated from other episodes by at least 5.0 min.

Other testing. All subjects maintained a diary of angina symptoms and nitroglycerin use for each treatment phase. Blood tests consisted of a complete blood count, platelet aggregation studies with ADP (adenosine diphosphate) and epinephrine, tissue plasminogen activator (tPA) antigen, tissue plasminogen activator inhibitor (PAI-1) and plasma epinephrine and norepinephrine levels.

Statistical methods. Baseline demographic variables were summarized for all subjects and by the three treatment sequence groups. Comparability between treatment sequence groups was evaluated using analysis of variance for continuous variable and chi-square tests or Fisher's exact test for categorical variables. Treatment effects were analyzed using one-way analysis of variance. The multiple comparisons procedure utilized for these analyses was Fisher's Least Significant Difference for multiple treatment groups. Pairwise comparisons were made if and only if the overall F-test was significant. Two-sided p values less than 0.05 were considered significant. The study had 82% power to detect a change in overall wall-motion score among the three treatment groups using an effect size of 0.047.

Results

Subject population. There were 17 subjects (16 male) of mean age 65.5 years (range 45–75 years). Angina duration was a mean 4.7 years, and five subjects were NYHA (New York Heart Association) class I, 11 subjects class II and 1 patient class III. There were no differences across treatment sequences regarding these demographic data. Fifteen subjects completed all phases of the treatment protocol, one dropping out owing to a myocardial infarction and another to patient preference. Statistical analyses were performed based on subjects completing all phases of the study protocol. Subjects were divided into two groups based on the change in overall ejection fraction in response to mental stress during placebo treatment: "Ejection fraction responders" (n = 5) with a decrease in EF of ≥5% and "ejection fraction nonresponders" (n = 10) with an increase or decrease of <5%. The treatment sequence for the five responders was nifedipine/atenolol/placebo (n = 3) and placebo/nifedipine/atenolol (n = 2). The treatment sequence for the 10 nonresponders was nifedipine/atenolol/placebo (n = 3), placebo/nifedipine/atenolol (n = 4) and atenolol/placebo/nifedipine (n = 3). Only one patient developed ST-segment depression during mental stress testing, and no subjects developed angina.

Changes in catecholamine levels, skin conductance and double product in response to mental stress. The results of serum catecholamine levels, skin conductance and double product in response to mental stress are shown in Table 1. Serum epinephrine levels rose in response to mental stress, although this increase was most prominent during placebo and atenolol therapy, with a statistically insignificant increase during nifedipine therapy. Serum norepinephrine levels rose significantly in all groups in response to mental stress. In addition, significant increases occurred in all subgroups in the degree of autonomic arousal as measured by changes in skin conductance at peak mental stress from baseline, but no significant difference occurred in the degree of arousal among treatment groups. Atenolol therapy was associated with a lower double product compared with placebo or nifedipine.

Changes in left ventricular systolic function in response to mental stress. *Global left ventricular function.* Overall, the mean global EF showed no significant change in response to mental stress during any treatment period (Table 2). However, when subjects were divided into groups based on changes in global EF during placebo therapy, there was a significant protective effect of both nifedipine and atenolol therapy in group 1 subjects: that is, these two medications prevented the fall in global EF noted during the placebo phase (Fig. 1). In group 2 subjects, there was no significant change in global EF associated with any therapy.

Regional left ventricular function. During placebo therapy, there was a highly significant mean reduction in semiquantitative wall-motion score and in regional EF in response to mental stress. On placebo therapy, eight subjects (53%) developed new regional wall-motion abnormalities, compared with six subjects during therapy with nifedipine and four

Table 1. Results of Mental Stress Testing: Changes in Skin Conductance and Catecholamine Levels and Double Product

	Placebo	Nifedipine	Atenolol	p Value	Pairwise p Values N/A	N/P	A/P
Skin conductance level (μS/cm^2)							
Resting Minimum	3.07 ± 2.02	3.07 ± 1.93	2.63 ± 1.45				
Δ Overall	5.44 ± 4.55‡	5.14 ± 3.29‡	4.06 ± 3.68‡	0.295			
Group 1	6.46 ± 5.83†	5.05 ± 2.91†	6.52 ± 6.21‡	0.422			
Group 2	5.09 ± 4.51‡	5.15 ± 3.78‡	3.12 ± 1.42†	0.191			
Epinephrine (pg/ml)							
Overall							
Baseline	36.55 ± 30.79	36.64 ± 22.29	41.07 ± 20.88	0.821			
Δ	16.64 ± 4.81†	8.09 ± 4.81	10.45 ± 4.81*	0.421			
Group 1							
Baseline	21.14 ± 20.19	30.20 ± 8.56	39.60 ± 26.10	0.300			
Δ	15.23 ± 6.27	2.34 ± 6.27	9.00 ± 6.27	0.432			
Group 2							
Baseline	45.11 ± 33.25	40.22 ± 27.03	41.89 ± 19.12	0.760			
Δ	15.98 ± 5.94*	10.88 ± 5.94	14.47 ± 5.94*	0.823			
Norepinephrine (pg/ml)							
Overall							
Baseline	232.20 ± 124.83	283.53 ± 115.09	188.93 ± 86.38	0.005			
Δ	137.38 ± 21.13‡	173.36 ± 21.13‡	123.26 ± 21.13‡	0.236			
Group 1							
Baseline	130.60 ± 43.73	198.80 ± 90.37	97.80 ± 45.92	0.178			
Δ	101.81 ± 31.53*	128.08 ± 31.53†	83.19 ± 31.53*	0.647			
Group 2							
Baseline	283.00 ± 121.61	325.90 ± 104.84	234.50 ± 61.22	0.062			
Δ	135.19 ± 28.09‡	179.66 ± 28.09‡	138.32 ± 28.09‡	0.017	0.005	0.077	0.180
Double Product (bpm × mm Hg)							
Overall							
Resting	9094 ± 5540	8783 ± 1847	6984 ± 1232	0.001	<0.001	0.258	<0.001
Δ	6696 ± 2552‡	6403 ± 3077‡	5303 ± 1685‡	0.053			
Group 1							
Resting	8706 ± 888	8507 ± 909	7294 ± 1209				
Δ	6395 ± 1465‡	5305 ± 1002‡	5203 ± 1953‡	0.71			
Group 2							
Resting	9184 ± 2704	8825 ± 2089	6659 ± 1095				
Δ	7061 ± 3150‡	7241 ± 3756‡	5700 ± 1538‡	0.115			

Group 1 denotes ejection fraction responders, and group 2 denotes ejection fraction nonresponders (see text). Δ = change. *$p < 0.05$. †$p < 0.01$. ‡$p < 0.001$ peak mental stress compared with baseline values.

subjects with atenolol ($p = 0.33$). When the segment with the greatest decrement in wall-motion score during placebo therapy was analyzed according to treatment group, both nifedipine and atenolol therapy prevented the mental stress-induced deterioration in wall motion observed on placebo (Fig. 2, $p = 0.009$, compared with placebo for both). Likewise, regional EF decreased significantly in response to mental stress during placebo (Fig. 2). Nifedipine therapy protected against this deterioration ($p = 0.01$) and atenolol therapy was associated with a trend toward protection ($p = 0.08$).

Changes in left ventricular diastolic function in response to mental stress. As shown in Table 3, when changes in diastolic function in response to mental stress were analyzed for the three different treatment groups, nifedipine was associated with improved peak filling rate on baseline (premental stress testing) compared with placebo, and there was a trend toward an improvement at baseline with atenolol therapy compared with placebo. No significant effects of atenolol or nifedipine occurred on the change (postmental stress minus premental stress) in peak filling rates or change in time to peak filling.

Changes in platelet aggregation, tPA antigen and tPA inhibitor in response to mental stress. No significant changes occurred in platelet aggregability to ADP or epinephrine or tPA antigen levels in response to mental stress. During nifedipine therapy only, there was a significant decrease in the level of tPA inhibitor in response to mental stress.

Results of exercise testing and ambulatory ECG monitoring. Except for lower resting and peak heart rate and peak double product on atenolol therapy, there were no significant differences in exercise test variables among treatments or when subjects were divided into groups based on global EF response to mental stress. Ischemia on ambulatory ECG (AECG) monitoring was infrequent, and there were no significant differences among treatments or patient groups in number of episodes or total duration of ischemia.

Table 2. Results of Mental Stress Testing: Radionuclide Ventriculography

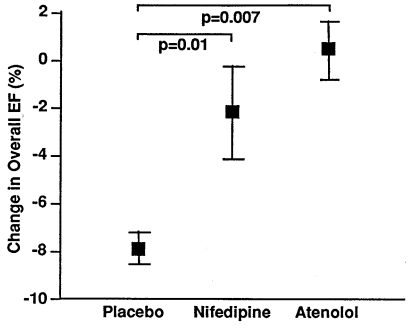
	Placebo	Nifedipine	Atenolol	p Value	Pairwise p Values N/A	N/P	A/P
Global ejection fraction (%): all patients							
Resting	58.33 ± 7.68	62.07 ± 8.36	61.80 ± 6.71	0.16			
Peak mental stress	57.07 ± 6.86	60.00 ± 7.58	59.93 ± 9.13	0.39			
Δ	−1.27 ± 5.64	−2.07 ± 5.04	−1.87 ± 5.63	0.94			
p Value	0.461	0.270	0.247				
Global ejection fraction (%): Group 1 Ejection fraction responders (n = 5)							
Resting	62.40 ± 1.52	62.80 ± 2.86	65.20 ± 3.56	0.07			
Peak mental stress	54.60 ± 0.89	60.60 ± 6.73	65.60 ± 4.51	0.01			
Δ	−7.80 ± 1.64	−2.20 ± 4.55	0.40 ± 2.88	0.01	0.56	0.01	0.007
p Value	0.001	0.59	0.75				
Global ejection fraction (%): Group 2 Ejection fraction nonresponders (n = 10)							
Resting	56.30 ± 8.77	61.7 ± 10.23	60.10 ± 7.40	0.07			
Peak mental stress	58.30 ± 8.23	59.70 ± 8.30	57.10 ± 9.69	0.01			
Δ	−2.00 ± 3.56	−2.00 ± 5.50	−3.00 ± 6.43	0.01	0.56	0.01	0.007
p Value	0.001	0.59	0.75				
Wall-motion scores: Segment with largest decrease during placebo phase (all patients)							
Resting	2.44 ± 0.63	2.13 ± 0.96	2.19 ± 0.91				
Peak mental stress	1.88 ± 0.96	2.13 ± 1.02	2.19 ± 0.83				
Δ	−0.53 ± 0.13	0.00 ± 0.13	0.00 ± 0.13	0.011	1.000	0.009	0.009
p Value	<0.001	0.99	0.99				
Regional ejection fraction (%): Region with largest decrease during placebo phase (all patients)							
Resting	58.53 ± 15.80	56.67 ± 17.88	57.80 ± 13.39				
Peak mental stress	44.87 ± 12.82	54.20 ± 16.20	52.80 ± 14.07				
Δ	−13.67 ± 10.25	−2.47 ± 9.32	−5.00 ± 12.58				
p Value	<0.001	0.513	0.062	0.034	0.366	0.011	0.081

Δ = Change from resting to peak mental stress.

Discussion

The catecholamine surge associated with mental stress may lead to transient myocardial ischemia either by causing coronary vasoconstriction or by increasing myocardial oxygen demand, and blocking either mechanism may be effective in preventing the development of ischemia. Our data suggest that both nifedipine GITS and atenolol are protective against deterioration in overall and regional wall motion associated with mental stress. Therapy with atenolol resulted in a lower resting double product as well as lower peak double product after mental stress, and hence atenolol may prevent wall-motion abnormalities by reducing myocardial oxygen demand. Nifedipine therapy improved regional wall-motion abnormalities without reducing peak double product, and thus may have prevented mental stress-induced coronary vasoconstriction.

Figure 1. Change in global ejection fraction: Subjects with a decline of ≥5% on placebo (n = 5). Boxes indicate mean values, with error bars demonstrating 1 SE unit. EF = left ventricular ejection fraction.



Mental stress induced changes in skin conductance and catecholamine levels. Our study followed the protocol developed by Jacobs and co-workers (31) using skin conductance as an index of autonomic arousal. Significant and similar increases occurred in skin conductance and plasma epinephrine and norepinephrine levels after mental stress for all three treatment phases, confirming that mental stress was adequately induced in these serial examinations to allow for comparisons among treatment groups (34). Using continuous monitoring of skin conductance, we were able to tailor the magnitude of mental stress to assure consistency of physiologic arousal within each subject on serial tests. This approach was used because therapy with nifedipine and atenolol did not allow the use of heart rate or blood pressure to gauge the degree of mental stress achieved.

Mental stress induced changes in global and regional left ventricular systolic function. Other investigators have shown changes in global left ventricular EF in response to mental stress similar to those we observed, with a minority of subjects showing significant decreases. For example, only 1 of 18 subjects in a study by Ironson and colleagues (6) demonstrated >7% decrease in EF in response to stressful speaking or

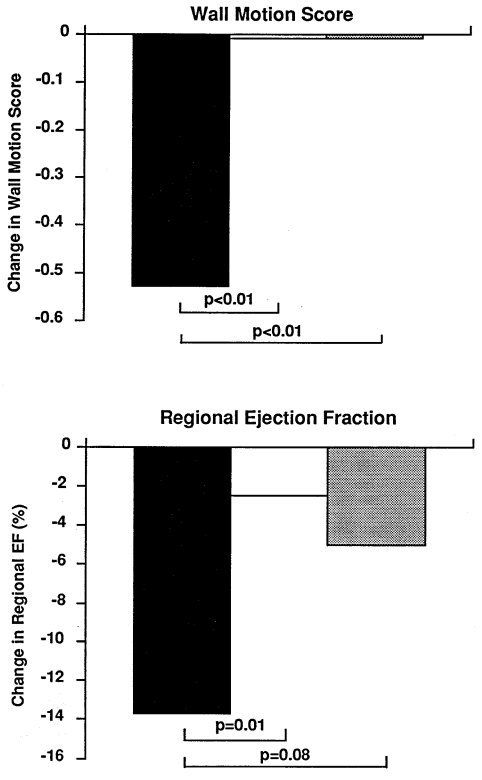


Figure 2. Change in wall-motion score and regional ejection fraction: Comparison of region with largest decrease during placebo phase for all 15 subjects. See text for explanation of wall-motion scoring and Table 2 for absolute values for wall motion and regional EF. Pairwise comparisons are not statistically significant unless otherwise indicated. EF = left ventricular ejection fraction. ■ = placebo; □ = nifedipine; ▩ = atenolol.

mental arithmetic. In the original study by Rozanski and colleagues (11), 59% of subjects demonstrated new regional wall-motion abnormalities, but only 14 of 39 (36%) of subjects had a fall in overall EF of at least 5%. We found that in five subjects with a decline in global EF in response to mental stress during placebo therapy, atenolol and nifedipine GITS were protective. In addition, when the segment with the largest decrement in regional wall motion or regional EF on placebo therapy was analyzed separately for all 15 subjects, nifedipine GITS and atenolol prevented the development of wall-motion abnormalities.

Mental stress induced changes in left ventricular diastolic function. In response to myocardial ischemia, changes in left ventricular diastolic function may precede deterioration in left ventricular systolic function and ECG ST-segment depression in patients with coronary artery disease (35,36). The effect of mental stress-induced ischemia on left ventricular diastolic function has not been previously studied. Although baseline peak filling rate was abnormal in our subjects, we were unable to demonstrate a further deterioration associated with mental stress, even when we separated subjects into groups based on changes in systolic function. There are several possible explanations for this negative result. First, our study may have lacked power to detect small but significant changes in diastolic function. Second, peak filling rate (PFR) is an index of global diastolic function and may therefore be a poor measure of regional diastolic dysfunction from regional ischemia. Third, PFR determined by radionuclide ventriculography is a measure of rate of change in volume and may not accurately reflect diastolic properties of the left ventricle in the absence of simultaneous measurements of pressure (37). It is possible that more sensitive invasive measurements would have detected changes in diastolic function in response to mental stress in our subjects.

Mental stress induced changes in platelet aggregation and fibrinolytic activity. Changes in platelet aggregability (38) and/or endogenous fibrinolytic activity (39–42) may be important in the pathophysiology of acute myocardial infarction, and the effect of mental stress on these parameters has been poorly studied. Perhaps owing to lack of statistical power, we did not observe changes in platelet aggregability in response to mental stress. Malkoff et al. (43) reported an increase in ADP secretion but no change in platelet aggregation to ADP in response to mental stress. Grigani and colleagues (44) reported a small increase in platelet aggregation to ADP associated with mental stress. We did not observe changes in tPA antigen levels associated with mental stress, although during nifedipine therapy mental stress was associated with a decrease in the level of PAI-1. These data are in contrast to those of Jern et al. (45), who demonstrated a small increase in tPA antigen and no change in tPA inhibitor associated with mental stress during placebo therapy.

Study limitations. Our study was limited by a small sample size that may have led to type II errors for some of the secondary end points. However, previous investigators

Table 3. Results of Mental Stress Testing: Radionuclide Ventriculography Diastolic Variables

	Placebo	Nifedipine	Atenolol	p Value	Pairwise p Values N/A	N/P	A/P
Resting (premental stress)							
TPFR (msec)	187 ± 15.3	177 ± 10.8	191. ± 16.0	0.76			
PFR (EDV/s)	2.01 ± 0.12	2.32 ± 0.15	2.13 ± 0.15	0.03	0.13	0.03	0.15
Δ (Postmental stress–premental stress)							
TPFR (msec)	20.0 ± 19.0	22.5 ± 11.7	−3.8 ± 11.4	0.44			
PFR (EDV/s)	−0.09 ± 0.10	−0.08 ± 0.13	−0.11 ± 0.09	0.96			

PFR = peak filling rate; EDV = end-diastolic volume; TPFR = time to peak filling rate.

(1,9,12,20,26,30) have utilized similar numbers of subjects, and the crossover design in our study increased statistical power.

Conclusions. Both nifedipine GITS and atenolol are effective in preventing the development of wall-motion abnormalities or overall left ventricular dysfunction in response to mental stress, though the two therapies display different mechanisms of action. Further studies are needed to determine whether combination therapy with atenolol and nifedipine is more effective than either agent administered as monotherapy in the prevention of mental stress-induced ischemia.

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